The Effects of Time-Delay on Feedback Control of Depth of Anesthesia

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***Abstract*— This paper presents a new procedure to find the impact of the time-delay (TD) of the patient and instrumentations such as bispectral index (BIS) monitor on closed-loop control of depth of anaesthesia during surgery. In the current work, the TD is estimated using Smith Predictive control technique. The method is validated with measured BIS signals in simulation. The results showed that the proposed procedure improves the performance of the closed-loop system for reference tracking and overall stability, and the proposed method has less overshoot, shorter settling time and is more robust to disturbances.**

I. Introduction

MEDICAL Medical experience with critically ill Medical experience with critically ill patients has revealed that standard dosing guidelines often result in an inappropriate under- or over-sedation which is leading to increased mortality due to huge inter-patient pharmacological variability [1], [2], [3].Open-loop control (manual control) by clinical personnel can be tedious, imprecise, time-consuming, and sometimes of poor quality. Hence, the need for active control (closed-loop control) in medical systems is significant, with the potential for improving the quality of medical care as well as curtailing the increasing cost of health care. During anaesthesia there is a time delay between the administration of the drug and the start of mixing in the central nerve system, estimation of the time delay is an important issue to closed loop control in surgery theatre [4], [5].

The Pharmacokinetic (PK) time delay is consistent for each individual patient, but can vary significantly between different patients. The origin of the time-delay (TD) is the period of time from the start of infusion pump until the drug is distributed along the central nerve system; the TD varies from one time instant to another, dependent on the signal quality. If not dealt-with appropriately, such varying TD are a source of poor feedback control [6]. This system is modeled as the open loop transfer function followed by a time delay represented using a 1^{st} order Pade approximation. The Pade approximants is used to approximate functions by rational functions [7]. A controller design technique is proposed based on a delay-dependent approach. The aim of this study is to establish and validate a TD estimation method using Smith Predictive to overcome the lack of TD information in online clinical trials for closed-loop sedation in surgery. To estimate the time-delay, some researchers have used the concept of the cross-correlation analysis, which is defined as estimation of the time-delay originated from instrumentation only (BIS monitor) during intensive care period [2] and, the estimated time-delay is then used in the prediction model of the extended prediction self-adaptive control algorithm (EPSAC).

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The paper is organized as follows: Section 2 introduces human body model for DoA. Section 3 describes materials and methods, Section 4 describes Smith technique and Section 5 provides simulation and results. The conclusions are drawn in Section 6.

II. Human Body Model for Depth of Anaesthesia Control

The patient body is divided into several compartments to drive the pharmacokinetic (PK) model [8]. In each compartment, the drug concentration is homogeneous as shown in Fig. 1**.** A three-compartment model is used, in which the main compartment represents intravascular blood (blood within arteries and veins) and highly irrigated organs (such as heart, brain, liver and kidney). The other two compartments represent muscles, fat, and other organs or tissues.

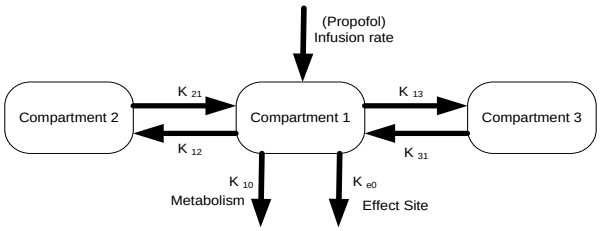

Fig. 1. PK compartments model.

The PK model provides the propofol plasma concentration from a given dose of propofol injected to the patient.

where PK is expressed as:

$$PK(s) = \frac{C_p(s)}{u(s)} = A\frac{1}{s+p_1} + B\frac{1}{s+p_2} + C\frac{1}{s+p_3} \quad (1)$$

where $C_p(t)$ is the drug concentration expressed in microgram per milliliter (propofol), p_1 and p_2 in the above formula would refer to the rate constant of the distribution phase and p_3 is the rate constant of the elimination phase.
where $u(s)$ is the control input.

PD is expressed as:

$$PD(s) = \frac{k_{e0}}{s+k_{e0}} + \frac{\gamma}{4EC_{50}} \quad (2)$$

where k_{e0} is the inverse of the effect-site compartment time constant and EC_{50} is the half-maximal effective concentration.

The Hill curve is represented by the following equation:

$$BIS(t) = E_0 - E_{max} \cdot \frac{{C_e}^{\gamma}(t)}{{C_e}^{\gamma}(t) + EC_{50}^{\gamma}} \quad (3)$$

E_0 denotes the baseline value (awake state) and by convention a value of 100 is assigned. E_{max} denotes the maximum effect achieved by the drug. C_e is the drug effect-site concentration, EC_{50} is the drug concentration at half maximum effect and represents the patient sensitivity to the drug, and γ determines the steepness of the curve.

The patient's PK and PD models are used to predict the BIS output as a result of drug infusion. The generalized PK–PD model for propofol is shown in Fig. 2.

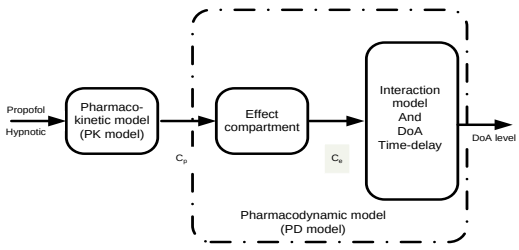

Fig. 2. DoA model

III. MATERIALS AND METHODS

The total time delay can be categorized into two parts. The first is related to the instrumentation parts, representing the time delays at the instrument devices and the second are related to the dynamic response of the patient (non-instrumentation delay).

A. Time-Delay estimation

During surgery, when the patient arrives at the ICU, the desired BIS target is 50 and must remain between 40 and 60 for a good sedation level. At around 50 BIS can be approximated linearly by a line, using this relation, as in

$$BIS(t) = a\,C_e(t) + b \quad (4)$$

where a represents the slope of the linear approximation and b is a constant.

The real values of the parameters for the selected 12 patient sets are given in Table 1 have been taken form reference [1] and simulated BIS signals were obtained based on the scheme presented in Fig. 3. The Propofol infusion is applied to the patient and the real BIS signal is recorded by the BIS monitor. As mentioned above, the monitor introduces a time-delay. The same Propofol infusion rate is used in the simulator to obtain the simulated BIS signal. Using the PK-PD patient model, the effective concentration of the drug is calculated. The simulated BIS signal is related to the effective concentration of the drug by the Hill curve. A delay is added to simulate the delay introduced by the real monitor.

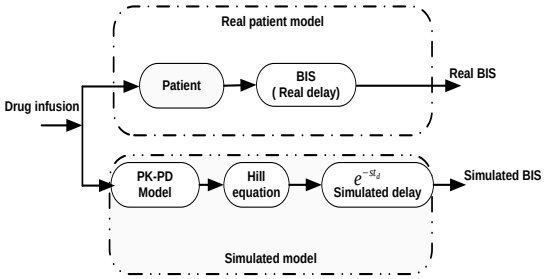

Fig. 3. The representation of the real and simulated BIS

With the time-delay introduced by the BIS monitor, the real BIS signal can be expressed by the following relation, as in

$$BIS(t) = a\,C_e(t-\tau) + b \quad (4-a)$$

SPC is a solution for controlling processes that present significant and varying dead times is to make use of a dead-time compensator (delays at the instruments). SPC provides a control strategy for linear processes with variable TD. The method of SPC was the first control system strategy proposed in the literature that included a dead-time compensator, and SPC is one of the most widely used methods to compensate the variable TD problem.

B. Identifying the PK time-delay

Inter-patient variability clearly plays a prominent role in the overall system uncertainty [9]. For instance, there is a significant difference in the PK time delay and PD time constant between patients. Also, while the EC50 variability is more limited, there is still a 6-times difference in terms of the overall PK-PD steady state gain [9]. The PD identification during induction, however, may not be practical due to a large number of factors that

can affect the anaesthesia time course [9].

One advantage of the SPC structure in case the PK time delay is known, is that there is no longer a need for a distinct controller for each patient. As far as the implementation of the SPC is concerned, the nominal time delay is now replaced by the identified time delay.

IV. Smith Predictor Controller for Depth of Anaesthesia

The Smith predictor controller is able to compensate for the dead time, through the use of a mathematical model of the process and its dead-time to feedback to the primary controller, what the process variable would have behaved without the delay. In addition, the performance of the SPC largely depends on the accuracy of the process model.

In systems with large delays, performance can also be improved by using a Smith Predictor Controller structure that compensates for the nominal time delay. This time delay compensation allows an increase in the controller bandwidth, which results in improved performance.

The Smith Predictor makes use of the nominal model of the system in order to compensate for the delay. The zero-delay nominal model is simulated based on the same infusion rate that is input to the system. As such, the model output represents the predicted delay-free response of the system. This response is then compared to the response with delay. The result of this comparison is a signal that represents the future system response to the control action. This signal is then added to the feedback signal. As a result, the controller can be designed based on a delay-free model, which results in added stability in the control loop that can be further used to increase the controller bandwidth. While the inherent limitation of a delayed system is still present, the increased control bandwidth usually results in increased performances.

The SPC proposed a control structure to compensate for the delay time shown in Fig. 4. By using this structure, the effect of the delay time in the system can be properly removed. As shown in Figure 6, $G_c(s)$ is the controller, the $G_p(s)$ denotes the transfer function of the patient without delay time and $\widehat{G}_p(s)$ is the estimation model of the system, t_p is the delay time of the patient, and t_m is the delay time of measurement. The transfer function is obtained in the following equation:

$$\frac{Y(s)}{R(s)} = \frac{G_c(s)G_p(s)e^{-t_pS}}{1 + \hat{G}_p(s)G_c(s) + G_c(s)G_p(s)e^{-t_pS} - \hat{G}_p(s)G_c(s)e^{-t_mS}} \quad (5)$$

In Fig. 4, the part of with the dotted line is the SPC and its transfer function obtained below:

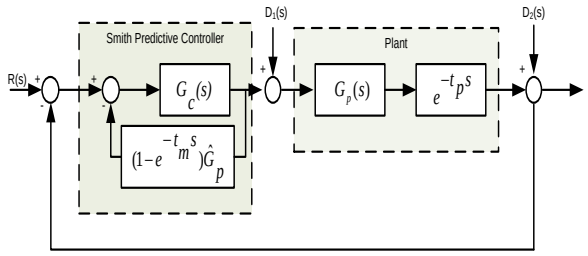

Fig. 4. The control structure with the Smith predictor

$$G(s) = \frac{G_c(s)}{1 + (1 - e^{-tmS})\widehat{G}_p(s)G_c(s)} \quad (6)$$

When $\widehat{G}_p(s) = G_p(s)$ and $t_m = t_p$ and then equation (2) is become:

$$G(s) = \frac{Y(s)}{R(s)} = \frac{G_c(s)G_p(s)}{1 + G_c(s)G_p(s)}e^{-t_pS} \quad (7)$$

where $G_p(s)$ is the patient model and consist of two parts, PK and PD [1].

Thus, the system will present the same closed-loop performance without the time delay, only with the pure input time delay t_p. The Smith predictor Controller is purposed when DoA delays are significant as $t_p = t_m$.

V. Simulation and Results

The study was performed on a data set of 12 patients from [1]. The parameters of nominal patient obtained for the pharmacokinetics model were $k_{10} = 0.119$, $k_{12} = 0.112$, $k_{21} = 0.055$, $k_{13} = 0.0419$, $k_{31} = 0.0033$, $k_{eo} = 0.349$, $EC_{50} = 2.56$, $\gamma = 2.5$, as shown in Table 1. The adjustment of the controller gains was made in a simulation way trying to get a smooth transitory and a stable response. For validation purpose, a representation of the real BIS signal "signal without time-delay" was built. A time-delay was added to the simulator in order to represent the delay introduced by the BIS monitor. Thus, after several trials adequate values for SP controller set values was tested in the whole population of the study with satisfactory results. Fig. 5 and 6 presents the evolution of the anaesthesia for three different patients. The controller parameters are adjusted depending on the error between the system output (BIS) and the model reference output defined for this closed-loop.

The delay signal is then added to the feedback signal. As a result, the controller based on a delay-free model, which results in added stability in the control loop that can be further used to increase the controller bandwidth. While the inherent limitation of a delayed system is still present, the increased control bandwidth usually results in improved performances. As far as the implementation of the SPC is concerned, the nominal time delay is now replaced by the identified time delay.

When a patient has significant time delay, it is quite common to augment the controller with a Smith predictor, a construction that removes the delay term from the characteristics polynomial of the closed loop.

TABLE 1 VALUES OF THE PARAMETERS FOR THE 12 PATIENTS SETS ARRANGED IN THE DECREASING ORDER OF THEIR BIS SENSITIVITY TO PROPOFOL INFUSION

	Parameter							
Patient no.	k_{10}	k_{12}	k_{21}	k_{13}	k_{31}	k_{e0}	EC_{50}	γ
(sensitive) 1	0.08925	0.084	0.06875	0.031425	0.004125	0.459	1.6	2
2	0.14875	0.14	0.04125	0.052375	0.004125	0.239	1.6	2
3	0.14875	0.112	0.04125	0.0419	0.004125	0.239	1.6	3.133
4	0.14875	0.14	0.04125	0.052375	0.004125	0.239	1.6	3.133
5	0.08925	0.084	0.04125	0.052375	0.002475	0.459	2.65	2.551
6	0.14875	0.112	0.06875	0.031425	0.002475	0.459	2.65	2.551
(nominal) 7	0.119	0.112	0.055	0.0419	0.0033	0.349	2.65	2.551
8	0.119	0.112	0.055	0.0419	0.0033	0.239	2.65	2
9	0.119	0.112	0.055	0.0419	0.0033	0.349	2.65	2.551
10	0.08925	0.084	0.06875	0.031425	0.002475	0.459	3.7	2
11	0.14875	0.112	0.06875	0.031425	0.002475	0.349	3.7	2.551
(insensitive) 12	0.08925	0.084	0.04125	0.052375	0.002475	0.239	3.7	3.133

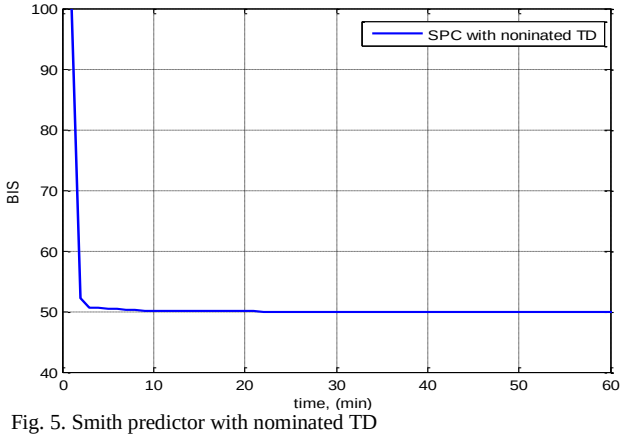

Fig. 5. Smith predictor with nominated TD

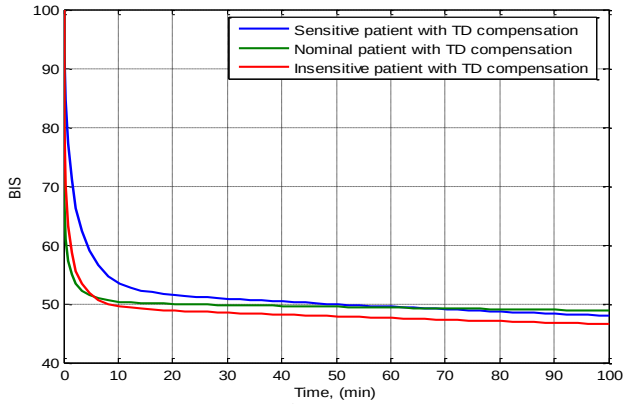

Fig. 6. Smith predictor with TD for 3 patients

VI. CONCLUSIONS

In this paper, the Smith Predictive Control has been introduced to estimate the TD originated from the patient and instrumentation (BIS monitor). The TD estimation algorithm is tested on a data set of 12 patients. The obtained results agree to similar studies reported in literature.

The estimation algorithms are based on the Smith Predictive Control. The improved time-delay compensation modules notably improve the performance of the overall patient response. These models have been implemented using Simulink and Matlab Control Toolbox and evaluated in simulation. The results have been compared to the control without time delay compensator. In the proposed system, the settling time has been shorten about 30% and the over and undershoot has been reduced about 15%.

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